

WE CLAIM:

1 1. A method for identifying a compound capable of interfering with
2 binding of an MRE11 polypeptide or fragment thereof, the method comprising the steps
3 of:

4 (i) combining an MRE11 polypeptide or fragment thereof with a
5 polypeptide selected from the group consisting of RAD50 and NBS1, and the compound,
6 wherein the MRE11 polypeptide or fragment thereof has nuclease activity and is encoded
7 by a nucleic acid that hybridizes under stringent conditions to a nucleic acid encoding a
8 polypeptide having an amino acid sequence of SEQ ID NO:2; and

9 (ii) determining the binding of the MRE11 polypeptide or fragment thereof
10 to a polypeptide selected from the group consisting of RAD50 and NBS1.

1 2. The method of claim 1, wherein the MRE11 polypeptide or
2 fragment thereof and the RAD50 or NSB1 polypeptide are combined first.

1 3. The method of claim 1, wherein the MRE11 polypeptide or
2 fragment thereof and the RAD50 and NSB1 polypeptide are combined.

1 4. The method of claim 1, wherein the MRE11 polypeptide or
2 fragment thereof and the RAD50 or NSB1 polypeptide are expressed in a cell.

1 5. The method of claim 4, wherein the cell is a yeast cell or a
2 mammalian cell.

1 6. The method of claim 5, wherein the MRE11 polypeptide or
2 fragment thereof is fused to a heterologous polypeptide.

1 7. The method of claim 1, wherein the binding of the MRE11
2 polypeptide or fragment thereof to RAD50 or NSB1 is determined by measuring reporter
3 gene expression.

1 8. A method for identifying a compound that modulates cellular
2 proliferation or chemosensitivity, the method comprising the steps of:

3 (i) contacting the compound with an MRE11 polypeptide, the polypeptide
4 encoded by a nucleic acid that hybridizes under stringent conditions to a nucleic acid
5 encoding a polypeptide having an amino acid sequence of SEQ ID NO:2; and

6 (ii) determining the functional effect of the compound upon the MRE11
7 polypeptide.

1 9. The method of claim 8, wherein the functional effect is measured
2 *in vitro*.

1 10. The method of claim 9, wherein the functional effect is a physical
2 effect.

1 11. The method of claim 10, wherein the physical effect is determined
2 by measuring substrate binding to the polypeptide.

1 12. The method of claim 9, wherein the functional effect is a chemical
2 effect.

1 13. The method of claim 12, wherein the chemical effect is determined
2 by measuring endonuclease or exonuclease activity of the MRE11 polypeptide.

1 14. The method of claim 8, wherein the polypeptide is expressed in a
2 eukaryotic host cell.

1 15. The method of claim 14, wherein the functional effect is a physical
2 effect.

1 16. The method of claim 15, wherein the physical effect is determined
2 by measuring ligand binding to the polypeptide.

1 17. The method of claim 14, wherein the functional effect is a chemical
2 or phenotypic effect.

1 18. The method of claim 17, wherein the chemical or phenotypic effect
2 is determined by measuring endonuclease or exonuclease activity of the MRE11
3 polypeptide.

1 19. The method of claim 17, wherein the chemical or phenotypic effect
2 is determined by measuring cellular proliferation.

1 20. The method of claim 19, wherein the cellular proliferation is
2 measured by assaying for DNA synthesis or fluorescent marker dilution.

- 1 21. The method of claim 20, wherein DNA synthesis is measured by
2 ^3H thymidine incorporation, BrdU incorporation, or Hoescht staining.
- 1 22. The method of claim 20, wherein the fluorescent marker is selected
2 from the group consisting of a cell tracker dye or green fluorescent protein.
- 1 23. The method of claim 8, wherein modulation is inhibition of cellular
2 proliferation.
- 1 24. The method of claim 8, wherein modulation is inhibition of cancer
2 cell proliferation.
- 1 25. The method of claim 8, wherein modulation is activating sensitivity
2 to chemotherapeutic reagents.
- 1 26. The method of claim 8, wherein modulation is activating sensitivity
2 of cancer cells to chemotherapeutic reagents.
- 1 27. The method of claim 14, wherein the host cell is a cancer cell.
- 1 28. The method of claim 27, wherein the cancer cell is a breast,
2 prostate, colon, or lung cancer cell.
- 1 29. The method of claim 27, wherein the cancer cell is a transformed
2 cell line.
- 1 30. The method of claim 29, wherein the transformed cell line is PC3,
2 HI299, MDA-MB-231, MCF7, A549, or HeLa.
- 1 31. The method of claim 27, wherein the cancer cell is p53 null or
2 mutant.
- 1 32. The method of claim 27, wherein the cancer cell is p53 wild-type.
- 1 33. The method of claim 27, wherein the cancer cell is treated with
2 bleomycin or etoposide.
- 1 34. The method of claim 8, wherein the polypeptide is recombinant.

1 36. The method of claim 8, wherein the compound is an antibody.

1 37. The method of claim 8, wherein the compound is an antisense
2 molecule.

1 38 . The method of claim 8, wherein the compound is a small organic
2 molecule.

1 39. The method of claim 8, wherein the compound is a peptide.

1 40 . The method of claim 39, wherein the peptide is circular.

41. A method for identifying a compound that modulates cellular proliferation or chemosensitivity, the method comprising the steps of:

(i) contacting the compound with an MRE11 polypeptide or a fragment thereof, the MRE11 polypeptide or fragment thereof encoded by a nucleic acid that hybridizes under stringent conditions to a nucleic acid encoded by a polypeptide comprising an amino acid sequence of SEQ ID NO:2;

(ii) determining the physical effect of the compound upon the SAK polypeptide; and

(iii) determining the chemical or phenotypic effect of the compound upon a cell comprising an MRE11 polypeptide or fragment thereof, thereby identifying a compound that modulates cellular proliferation or chemosensitivity.

42. A method of modulating cellular proliferation in a subject, the method comprising the step of administering to the subject a therapeutically effective amount of a compound identified using the method of claim 8.

43. The method of claim 42, wherein the subject is a human.

1 44. The method of claim 43, wherein the subject has cancer.

45. The method of claim 42, wherein the compound is an antibody.

- 1 46. The method of claim 42, wherein the compound is an antisense
2 molecule.
- 1 47. The method of claim 42, wherein the compound is a small organic
2 molecule.
- 1 48. The method of claim 42, wherein the compound is a peptide.
- 1 49. The method of claim 48, wherein the peptide is circular.
- 1 50. The method of claim 42, wherein the compound inhibits cancer cell
2 proliferation.
- 1 51. A method of modulating cellular proliferation in a subject, the
2 method comprising the step of administering to the subject a therapeutically effective
3 amount of a MRE11 polypeptide, the polypeptide encoded by a nucleic acid that
4 hybridizes under stringent conditions to a nucleic acid encoding a polypeptide having an
5 amino acid sequence of SEQ ID NO:2.
- 1 52. A method of modulating cellular proliferation in a subject, the
2 method comprising the step of administering to the subject a therapeutically effective
3 amount of a nucleic acid encoding a MRE11 polypeptide, wherein the nucleic acid
4 hybridizes under stringent conditions to a nucleic acid encoding a polypeptide having an
5 amino acid sequence of SEQ ID NO:2.